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'Becoming-with' a repeat healthy volunteer: Managing and negotiating trust among repeat healthy volunteers in commercial clinical drug trials

Shadreck Mwale

Department of Clinical and Experimental Medicine, Brighton and Sussex Medical School, BSMS Teaching Building 216, University of Sussex, Brighton, East Sussex, BN1 9PX, UK

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ABSTRACT

Recent sociological research has raised important sociological and ethical questions about the role of financial rewards in terms of healthy volunteer involvement in clinical trials. Research suggests that it would be parochial to assume financial rewards alone are sufficient to explain repeat healthy volunteering. This paper explores other factors that might explain repeat healthy volunteering behaviours in phase I clinical drug trials. Drawing on qualitative research with healthy volunteers, the paper argues that while healthy volunteers make rational decisions to take part in drug trials, understanding how they become repeat volunteers requires considering varied relationships and networks involved. Drawing on Deleuze's concept of 'event' and 'becoming-with', the paper illustrates the relational, processual and embodied nature of trust in repeat healthy volunteer involvement in clinical drug trials. The paper concludes that repeat healthy volunteering is a constant flux of negotiating trust and mistrust. The paper contributes to sociological debates about trust and public engagement with technological innovations to illustrate trust among healthy volunteers as processual and changeable.

1. Introduction

Clinical drug trials are globally established as the standard for ensuring safety and efficacy before marketing medical drugs. The procedure involves complex and elaborate processes (Rajan 2006). Pre-clinical phase, tests for iterative toxicity and drug safety data collection, often involves animal testing followed by a further four phases in humans. Phase I - the focus of this paper - involves testing investigational medicinal products (IMP) on a limited number of healthy volunteers to ascertain safety and determine minimum and maximum dosages to be administered with no health benefit from participation. IMPs can involve drugs already on the market being reconsidered to treat other conditions. In Phase II, the drug is tested on more substantial numbers to determine further efficacy and optimal dosages. Participants again experience no discernible benefit. Phase III involves several thousand patients with the condition for which the drug is developed; IMP is tested for safety, efficacy, and therapeutic potential. The fourth phase, is post-marketing surveillance, comparing the IMP's effectiveness in a wide range of patients with the same condition (see Petryna, 2009; Pocock, 2013).

With heightened public demands for novel treatments (Petryna, 2009), clinical drug trials are increasingly taking place across the UK, requiring more participants. Between 2005 and 2016, the Medicines and Healthcare Regulatory Authority (MHRA) reviewed approximately

11,473 Clinical trials applications. Of these, 2702 were for phase I clinical trials (MHRA, 2018). For these trials specifically, participation has been attractive not only to those involved in the drug development processes, such as Contract Research Organisations (CROs) (Shuchman, 2007) but to healthy participants. Recent sociological research has shown how for some healthy volunteers participation is a means for earning or supplementing income (Abadie, 2010; Fisher and Kalbaugh, 2011; Mwale, 2017; Walker et al., 2018). Alluring rewards have led some to participate in multiple drug trials simultaneously. This tendency risks the study's integrity; participants' blood may contain remnants of drugs from one trial that interact with the experimental drug in another, compromising outcomes and posing a risk to the participant's health (Abadie, 2010). However, healthy volunteers still participate, some deceiving research teams by not declaring histories of involvement (Dresser, 2013; Monahan and Fisher, 2015). This poses several challenges for clinical drug trials: Companies are concerned about reputation if unexpected adverse effects occur, compromising the methodological integrity of the trial, and risks to the safety and wellbeing of the participants. Concerns about healthy volunteer safety and public perceptions mean repeat-volunteering attracts professional and policy attention. Research Ethics Committees and similar structures are considered spaces for ensuring continued public trust in clinical research (Hedgecoe, 2014; Hudson et al., 2016). However, these alone are insufficient in explaining how public trust is developed and maintained in

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clinical drug trials.

Consequently, repeat healthy volunteering, the tendency of healthy volunteers to frequently enroll in clinical drug trials without leaving enough trial drug wash out period, has taken political and policy centre stage, particularly in the face of recent tragedies. In 2016 in France, one participant died and several dozen were admitted to hospital after suffering severe unexpected side effects. Ten years prior in London, six healthy volunteers suffered life-changing cytokine release syndrome with multi-organ failure after being infused with a monoclonal antibody in a clinical trial (Hedgecoe, 2013; Mwale, 2016; Abadie et al., 2019). Such events have raised public disquiet about safety, however, increasing numbers of people repeat volunteer, sometimes indiscriminately (Hale, 2007; Abadie, 2010; Monahan and Fisher, 2015). Concerns have led to increased regulatory measures such as The Over-volunteering Prevention Strategy (TOPS) installed to facilitate tracking and curb indiscriminate repeat volunteering (Allen et al., 2017). Its effectiveness is highly contested in the CRO community (Berelowitz and Taubel, 2013) and this debate is beyond the scope of this paper. However, the installation of this measure signals the significance of the challenges repeat volunteering poses to the business of clinical drug trials.

This paper explores how participants rationalise repeated involvement in clinical drug trials and negotiate and manage questions of trust when health and safety cannot be guaranteed. While financial incentives are usually the central motivating factor, repeat volunteering is based on a set of relationships and experiences within the process that facilitate the development of trust. Healthy volunteers draw on interactions with professionals, social networks and bodily experiences to become repeat volunteers. Research has focused on the need for improvement in institutional practices such as information provision and informed consent. However, there is little attention to individual considerations when engaging with institutions or practices within and outside these processes. Drawing on interview data with 35 healthy volunteers in the UK and using concepts of 'becoming-with' and 'event' the paper shows how networks and relationships bring about a constant negotiation of trust and mistrust. I argue that trust is crucial to the practice of repeat healthy volunteering and is mediated by both relations and institutionalised process of consent in the clinical drug trial process.

2. Trust and human entanglement with medical practices

Following watershed incidents such as the Nuremberg (Marks, 2006) and Tuskegee (Brandt, 1978) experiments, trust has been at the centre of policy and public debates about medical research for decades. Debates centre on the need for building trust between patients and medical professionals (Calnan and Rowe, 2007; Brown et al., 2011) and transparency to ensure continued public involvement in medical research (Mechanic, 1996). Trust in these settings is concerned with ensuring patients make informed decisions, including avoiding the possibility of therapeutic misconceptions (Appelbaum et al., 1987) whereby patients, as participants in medical research, should be explicitly informed about the non-therapeutic nature of clinical trials. Questions of trust in medicine and medical research remain of concern.

Where trust in clinical drug trials concerning healthy volunteers is discussed, this focusses on implications for trust in research processes in the aftermath of unexpected adverse incidents. Concerns relate to institutional practices and how these could be improved to retain public trust (O'Neill, 2002; Hedgecoe, 2013). In the US, ethnicity shapes public attitudes to biomedical research; African Americans are thought to be the least trustful of biomedical research due to the historical abuse of minority groups illustrated by the infamous Tuskegee experiment among others (Corbie-Smith et al., 2002; Brown and Topcu, 2003; Katz et al., 2003; Bates and Harris, 2004; Wendler et al., 2005; Durant et al., 2011). For those participating in uncertain research, whose outcomes or effects cannot be assured, they might require to draw on 'readily

available resources such as relationships, feelings and intuition' (Alaszewski and Coxon, 2009; 201), to establish and sustain trust or distrust.

Elliott (2008) found that healthy volunteers shared information when felt they were not treated respectfully; this information was astutely used by others in decision-making to avoid enrolling in Clinical Trials Units (CTU) with poor records of care, illustrating how trust is about social relations between volunteers and CTUs. Significantly in Elliott (2008) participants did not focus on experiences of unexpected adverse effects but on the quality of interpersonal relationships and facilities. They also reported on the quality of care such as poor blood taking skills (Elliott, 2008). Reference to professional skills is essential, highlighting the embodied nature of clinical trials and personal sense of safety and trust in the team's abilities. It appears that repeat participation is contingent on participants' perceived positive experiences and relationships. Elliott (2008) concludes that unless participants feel they have no choice, they will not go back to a facility where they had negative experiences. Trust is embedded in a complex set of collective relations and as an individual, social and institutional process involving both relational and cognitive processes.

3. Repeat volunteering as rational action: ensuring trust in clinical trials

Current approaches to public involvement in medical research can be traced to the Helsinki declaration. This signifies a key moment in the history of clinical trials, highlighting the impact of abuse and need for human rights in medical research (GAWMA, 2014). Whilst there have been numerous failings (Hedgecoe, 2017), a thrust of the declaration was the need to end paternalistic practices in clinical trials, encourage agency and restore public trust by ensuring voluntary involvement and informed consent. Today, these processes are established emblems of good research and a basis for public trust. Influenced by classical economic assumptions of individuals as rational actors (Becker, 1963), participants in clinical drug trials are construed as capable of making rational decisions, weighing benefits and risks. Trust is addressed by providing information and ensuring transparency. Risk is seen as an objective issue resolved by research ethics committees who weigh potential risks posed by the trial drug against the broader benefits. This approach is imbued with Bentham's (1996) classic utilitarian ideal of the greatest utility for the greatest number, tying into ideas of non-maleficence and beneficence (Beauchamp, 2008), cornerstones of ethical medical practice. Public trust in health professionals is predicated on their moral obligation to do good while the public needs to participate in research for the benefit of the greater good. Underpinning this approach are notions of rational and capable subjects.

Social science research into trust in medical settings has mostly taken psychological (Glaeser et al., 2000) and political science (Blais and ST-Vincent, 2011) approaches, trust understood through the lens of individual liberty and rational choice. This archetypal perception of human actors is in keeping with what Giddens (1991) terms a rational self in reflexive modernity, evident in bioethical principles' emphasis on individuals and their liberties. Information provision is seen as the basis on which trust is developed and maintained, as individuals make informed decisions through access to information. The limitation of this view is that it presents a universal model of the rational individual which negates the complex multifaceted nature of social realities of trust (Lewis, 1985). Corrigan (2003) challenged these assumptions, arguing that overemphasis on the fully informed rational individual divorces the consent process from its social context and negates the role of social networks in everyday medical encounters, risk perception and decision-making. O'Neill (2003); Hedgecoe (2004); Dixon-Woods et al. (2007) and Felt et al. (2009) indicate limitations of information provision in resolving all ethical questions in medical research; instead they call for an approach to informed consent that takes complexities into account.

While medical literature (de Balicourt and Dobsworth, 2013; Kahan et al., 2016) presents trust as an objective issue resolved by transparency, a sociological perspective considers how understandings of trust are produced, embedded and contoured by a complex set of social relations and processes (Brown and Gale, 2018) imbued with competing, contradictory power relations and demands (Braidotti, 2013; Dennis, 2017). Understanding trust in clinical drug trials requires going beyond information provision to include relational and processual elements as recent work on drug use has shown. Keane (2003) and Dennis (2016, 2017) question approaches to substance misuse focussing on rights and abilities. They argue it reduces complexities to anthropocentric experience removed from the multiple parties and processes involved. Though a different issue, there are parallels between injecting drug use and healthy volunteering; both pose risks to individual health with uncertain outcomes. Rather than focussing on rationality and individual rights, shifting the analytical gaze to broader contexts and relations enables prospects for understanding nuances of trusting among repeat volunteers, regardless of what study protocols may suggest. To a significant extent, involvement in clinical trials is at one's own risk. Participants put their trust in the abilities and intentions of administering professionals. Understanding how participants rationalise perceived risks and decisions to act as repeat volunteers requires utilising an approach to trust that considers the diverse networks and assemblages in which healthy volunteering takes place.

4. Theoretical framework

In this paper trust is explored as a relational, processual and embodied formation requiring constant negotiation and management. To better understand how healthy volunteers develop trust to become repeat volunteers, I draw on Deleuze's concept of the 'event' and 'becoming' to illustrate the embodied and connected nature of trust. As Law (2009) and Latour (2005) argue, a relational approach to bodies shows that actors are not inherently rational and capable of agency. Instead, individual action emanate from specific associations of networks that 'spatially and temporarily link one actor with another' (Duff, 2014). Therefore, an act of individual agency to trust or not to trust should be understood as entanglement with multiple bodies. This is not to suggest that all actors have the same experiences, as actors' capacities differ depending on the nature of the encounters and relations they have in the clinical trial process. In a Deleuzian sense, individual bodies act as "conduits" through which individual agency is produced, distributed and used (Armstrong, 1997). Trust is not a single-moment issue but processual, embedded in networked relations with humans and non-humans. For Deleuze, relations are about how the body and its encounters 'become' composed with the affects of other bodies; individual subjectivity should not be seen as isolated but embedded in a situated assemblage of diverse connections. Relations, therefore, are about embodied subjectivity situated in multiple relations with affect at the core, bringing bodies together in subjective experiences and encounters with the affect of other bodies (Duff, 2014; Dennis, 2017).

For Deleuze, the event signifies the transformation of bodies and subjects in the specific relations in which they are involved; 'becoming' and 'events' are ontologically prior to being, thus subjectivity and experiences are processual rather than fixed. Applying this view to healthy volunteer involvement in clinical trials, the clinical trial as 'event' involves the specific status of observable affairs '*in the comingling of bodies within and outside [the clinical drug trial units], and the incorporeal transformation rendered in such bodies by the event*' of the clinical trials with its related activities and processes (Duff, 2014; 46; Marks, 1998). Becoming pertains to those moments in which individuality comes into being, requiring an approach '*underpinned by a relational and processual ontology, with the human always caught in the ebbs and flows of becoming*' (Dennis, 2017; 340). Fraser (2011) analysis of the 'event' in STS and Deleuzian philosophy identifies two versions, one where the event is defined as 'being with', where the components of

the event 'co-habit' as the event proceeds, interacting with, and remaining unchanged in relation to one another. The other event is characterised as a 'becoming-with' as the components mutually change, or intra-act (Michael, 2015; Dennis, 2017). This paper draws on the latter.

I draw on Duff, 2012, 2016; Dilkes-Frayne (2014); Race (2015) and Dennis (2017) on injecting drug use; they apply the concept of the 'event' and 'becoming-with' to understanding injecting drug use, contending that attention should be shifted from 'who acts' to 'what occurs'. Here, drawing on Deleuze brings into focus a different question – 'what becoming-with' occurs in the clinical drug trial as an 'event'. As Dennis (2017; 340) posits, '*The hyphen in 'becoming-with drugs' is vital as it highlights that there are no pre-defined bodies – 'the body' or 'drug' – but these come to 'matter' (in its dual sense) in relation to each other*'. Parallels can be drawn with clinical drug trials as healthy volunteering occurs in a complex set of relations involving technology, drugs, institutional processes and individual bodies coming together in the trial, shaping and influencing each other. 'Becoming-with' refers to a continuous state that is not pre-defined or bounded but in constant flux. In Dennis' (2017) reading of Stagoll (2010), '*the event is not a disruption of some continuous state, but rather the state is constituted by events "underlying" it that when actualised, mark every moment of the state as a transformation*' (2010: 90). Central here is acknowledgement of the relational nature of encounters in the event and how they shape each other. Therefore, what may be understood as individual informed action is a product of multiple continuous relations.

5. Method

This qualitative research study aimed to investigate ethical and regulation dimensions of healthy volunteer involvement in the UK. The study involved semi-structured interviews (Kvale, 1983; Mwale, 2014) with 35 healthy volunteer participants in clinical drug trials. Semi-structured interviews obtained in-depth understandings of the motivations and experiences of healthy volunteers in commercial phase I clinical drug trials. Participants were resident in Belfast, Edinburgh, London, Leeds Liverpool and Manchester.

A survey questionnaire was used as a recruitment tool. Respondents were invited to give contact details to take part in interviews. Of 189 respondents 50.3% (95) expressed willingness to participate in interviews and 13.2% (25) of the 95 were interviewed. The 25 were recruited on the basis that they were looking to participate or had participated in one or more clinical drug trials. A further 10 participants were recruited via snowballing. All but one participant were in employment at the time of interview. Participants whose data are used in this paper had participated in at least one clinical drug trial. Experiences of clinical trial involvement ranged from one to ten or more.

Interviews were face-to-face apart from two telephone and two skype interviews for participants who were unavailable for face-to-face meetings. Interviews took place at participants' convenience and were conducted in public spaces such as cafés, parks or similar places for comfort (Mwale, 2014) lasting on average 60 min. Interviews explored motivation, views of monetary rewards, risks, their interaction with research, experiences of adverse effects, and how their involvement in clinical trials shaped perceptions of their bodies. Interview length ranged from 25 to 90 min, with the majority lasting over an hour.

Interviews were recorded and transcribed verbatim. Data were analysed using a thematic analysis approach (Braun and Clarke, 2006). This approach involves a six-step process involving familiarisation and immersion in the data by reading and re-reading to enable intimate understanding of the material. A search for themes follows before coding the data, identifying characteristics to enable answering the research questions being explored. Codes are further analysed and refined and finally, themes and data extracts are woven into a narrative in relation to the literature. This provides flexibility in that while

questions direct data analysis, it allows for new ideas and themes to emerge. Combining thematic analysis and a Deleuzian approach enabled going beyond the 'individual' to consider relational aspects of bodies. Participants were fully informed and assured of their rights to withdraw or not to answer any questions they found uncomfortable. Identities of all participants and organisations involved are anonymised. Ethics approval was obtained from the University of Sussex Arts and Social Science ethics review committee.

6. The toss-up: fragile trust as a point of departure

If they have not tested the drug on anyone? While I think it is important ... that drugs are tested thoroughly before they are made available to the wider public, I think there is a toss-up in selling your health and whether your health is ever worth any amount of financial compensation that you may get from taking part in the trial, because you can never be 100% sure ... [of the outcome of the drug trial] (Shivaune)

Shivaune's account demonstrates a common issue healthy volunteers contend with during the early stages and for some throughout their involvement in clinical drug trials. Healthy volunteers become involved while remaining sceptical about the processes. Shivaune uses the 'toss-up' analogy to highlight uncertain outcomes, potential risks to the participant's health and sufficiency of the financial rewards on offer. The participant's description demonstrates awareness of the risks involved, albeit based on incomplete knowledge as researchers do not know yet the effects of the drug, hence the purpose of conducting trials. This feeling of mistrust was not only about the experimental drugs but extended to healthcare professionals themselves:

For me the most concern was even if I trusted the guys [professionals administering the trial], how can I know this is the drug they describe on paper and the effects they say it has? What if they write one thing on paper and give me another drug? ... In the end, I had to convince myself that it is not possible, but even then, I struggle with that question every time I go into a clinical trial ... (Marko).

This illustrates that although providing information to participants is useful in aiding the consent process, analysis should go beyond normative consent procedures to consider the diverse human relations in which trust develops. Marko suggests that professionals may lie to him, illustrating tensions between trust and not-trusting, and how this is mediated by broader concerns. Information provided was subject to the same mistrust as the clinical trial process itself. However, it should be highlighted that despite these reservations Marko, at the time of the interview, had taken part in more than ten clinical drug trials.

For others, mistrust is underpinned by views and comments of wider networks such as family and friends who may see involvement in clinical trials as a risky endeavour. For Elliot, this was significant in his decision to participate in the first trial.

My mum said, "Don't be stupid, it's a silly idea. It's reckless. You will make yourself ill and there is no need for you to do that". I tried explaining that it was safe ... in a way there was an undertone that I should do something productive with my time [rather] than getting myself involved in clinical trials. "Get a job or something" (Elliot).

Yeah, I told them [the family] once. They were a little bit afraid for me; they did not have a lot of the facts. I think they just heard it's a trial and they were scared. My dad asked me to go back home if I was having problems with money. He will look after me, he said ... [Hank].

Despite policy attempts to improve public perceptions of clinical trials, public mistrust remains. Questions of trust or mistrust are equally shaped by social networks and proximity of risk. In the above account, the immediate family seemingly aids mistrust even when the participants had managed their concerns about the clinical drug trial. Elliot

did not take part in any further trials as his family could not accept his decision to be a healthy volunteer. For Hank, family views meant that he always took time to research drugs to be trialled so he could explain this and ease their reservations. However, Hank also positions his family as not knowledgeable enough in justifying his decision to participate. Therefore, attention should be paid to affect and how decisions to proceed against family advice often brought feelings of guilt while simultaneously family's deficit in clinical trial knowledge can be used to justify decisions. Trust should be viewed beyond making sense of expert information provided in participant information sheets as in negotiation with wider social, family, expectations. Trust among healthy volunteers shifts from being perceived as an issue resolved by routinised and taken-for-granted practice of information provision to a complex social event. Though information provision is essential, broader social networks enable interpretation and validation of decisions.

For other participants, trust as an assemblage is illustrated in an awareness of connections between the drug trial process, humans and non-humans, who are used in this process as human substitutes.

Initially, I thought, "I can't do these because the risk is too high". I know it may have been tested say, on animals like rats [and] monkeys or whatever but the human body is different ... You know, everybody has different enzymes and every species has different ways of dealing with drugs, so what may happen in a dog may be different to what may happen in humans, can't be replicated in humans (Jamie).

Therefore, trust in the trial manifests beyond human roles. Jamie questions the role of non-human actors as an information source and confirmation of the safety of clinical drug trials. This moves the common conception of healthy volunteering as a bounded event based on scientific facts to a fluid process in which participants consider multiple, competing and contradictory sources of information to negotiate questions of trust. After Deleuze (2004), trust in clinical drug trials involves negotiating the constant vacillation between trusting and not-trusting, management of uncertainties of outcomes and social perceptions of acceptable risk-taking. Therefore, trust is not just born out of an objective scientific process but understood best when located in an array of social relations, human and non-human, including technology:

When I started I was like "I don't want to be a complete guinea pig" the animals can be, so I googled about the drug content and the institution. So, I started with drug trials of drugs already in use, but with time I have found myself doing more very first phase drug trials ... (Cullum)

The first trial ... I had already done all the research online [note the role of information technologies] and a friend is a chemical engineer, so I knew there wasn't anything really to worry about in terms of anything going wrong. ... I could have trusted them and just took their word for it like that. I was not sure [I could] (Lauren)

This indicates tensions between scientific facts and tacit knowledge. Participants expressed caution when embarking on participation in clinical trials. Concerns about inherent risks led others to take evasive steps including participating in what they deemed low-risk studies, often trials of drugs already on the market. For some, this involved conducting further research via social networks or ICT sources to establish the safety of the experimental drug. As Jarret (2015) and King-O'Riain (2014) state, ICT technologies should be seen as relational artefacts to which and through which relations with self and others are mediated and established. Participants used ICTs not only for information (Miller, 2008) but as spaces for verifying and relating to self when making decisions that are seen as private, regardless of perceived inaccuracies. More than cognition and interpretation of a participant information sheet, affect and social relations shape decision-making processes. The internet is a site of more than 'disembodied rationality',

rather it is a space 'for physical arousal, heightened emotion and the cultivation and maintenance of rich social relationships' (Jarret, 2015; 121). Using ICTs, social networks and attendant affects, participants create their own knowledge practices (Orlikowski, 2002) as a basis for their trust.

Becoming trusting then involves considerable uncertainty and disorder rather than routinised consent processes. As Corrigan (2003:787) observes 'arguments that focus on informed consent as an absolute moral principle result in a reductionist abstraction and empty ethics that strips the principle of consent away from its social context'. Understanding repeat involvement in clinical drug trials requires considering the role of information provision and social contexts with the constant management and negotiation of risk perception on the one hand while on the other managing and justifying one's healthy volunteer status. Therefore, trusting becomes an assemblage of intricately bounded processes in which technology, non-human actors and human relations interact to bring about the act of participation.

Healthy volunteering becomes an involved process, disrupting the borders of real facts (scientific) and knowing (subjective epistemologies) (Corrigan, 2003; Dennis, 2017). Reference to 'the first trial' or 'the start' suggests that for these participants, trusting or not-trusting shifts over time. In terms of 'becoming-with', trust does not develop solely from a fixed set of relations such as information provision but includes wider social relations. Trust takes diverse meanings at different times, shaped by relationships in these encounters.

7. 'Becoming-with' a 'seasoned' repeat healthy volunteer

Trust among healthy volunteers should not be seen as an objective process with a capable calculative rational individual, willing to take risks. Rather I suggest an awareness of the complex, fluid nature of trust involving negotiation of a complex set of relations and interests. Here, I appropriate Dennis' (2017) reading of Deleuze's idea of 'becoming-with' to refer to the fragility and contingency of trust among healthy volunteers. 'Becoming-with' a healthy volunteer is a complex process; in addition to making sense of varied information, it requires willingness to manage corporeal discomforts and dehumanising experiences:

... to them we were just numbers on hospital beds and not people. It's quite strange, not that it was obvious, but in subtle ways. But you know, it (being on the trial) does really feel that you are just a specimen on trial (Shivaune).

... once you enrol, you become just a number; you are just there, you are not you. So it can be quite hard to deal with sometimes, and the powerlessness as well ... because basically to them you are just data, you know, but have value in the form of data and the money it represents, not the human being I am ... (Jake)

This illustrates a familiar feeling among these participants, demonstrating that to become a volunteer, one has to be willing to be seen as an item in the clinical drug trial process. For most participants, the first lesson on their healthy volunteer journeys was an acknowledgement that the body has become a mere object in the process. Becoming-with a healthy volunteer involves being able to manage the tensions between being yourself and being 'othered' (Jensen, 2011). The idea of being othered can be a shock to those just starting on their clinical trial journey, as illustrated by Dominique's experience: '... to start with its the change in the treatment when you are on the ward for the trial. It can be a shock ... when suddenly staff who were friendly start to refer to you as a number..'. This also illustrates that becoming-with a healthy volunteer inadvertently requires managing complex power relations. To repeatedly participate, one has to undergo a transformational process of managing the consequences of being treated as the other. The Clinical Trials Unit as a space for surveillance and control becomes apparent as participants have to abide by set rules, including eating, sleep times and what items one is allowed to bring in: 'I couldn't

have my make up on or walk outside-you are confined in this space' (Shivaune).

It requires developing the ability to withstand the inconveniences of needle pricks, interrupted sleep and unexpected adverse drug effects. As Jon suggests: 'doing this [clinical drug trials] as often as I have you become seasoned or more experienced if you like, able to cope [with the challenges posed by the trial]'. This identifies the role of external factors alongside the experience of managing affect and the corporeal experiences of adverse drug effects. It is learning to cope with these factors that facilitates becoming 'seasoned' and experienced as illustrated by Mia: '... you cannot do this if you want comfort, you register to know this will be uncomfortable ...' or as another participant elaborates, describing a fellow participant who was not coping with the pressures, '... She was always bitchin ... and complaining about everything from 6 to 6. We had a few words ... because you see, if someone decides to come on a trial, you must be ready for what it brings' (Jules).

For Jules 'becoming-with' a 'seasoned' volunteer requires an ability to manage feelings and endure associated inconveniences and discomforts. Not reacting to discomforts and managing affect become markers of a 'seasoned' healthy volunteer, indicating a transformation from inexperienced to experienced healthy volunteer. However, there is a contradiction in Jules account; while complaining is disallowed, constant uncertainty and anxiety is also referred to. This suggests that the transformation implied does not mean guaranteed future involvement in clinical trials without worries about risks. To appropriate Dennis's (2017) conception of transformation, who states the concept often invokes a sense of fixed stability. However, stabilising should not be seen to refer to coming to a fixed state, but indicates how these experiences are continuous part of formation and play a significant role in preparations and feelings about future drug use.

Healthy volunteers transforming into 'seasoned' volunteers may not entail a stable process, rather it is a continuous process in which questions about whether to trust professionals, institutional processes and one's worth arise in different ways. Significantly, alienation feeds participants' mistrust in the process: '... it's not that you [stop] finding it unsettling it's just that you find ways of coping with the challenges I guess. I often focus on the reward at the end ... so it's not like I am completely used [to doing it] ...'. Contingency of trust and role of affect is illustrated in the uncertainty around the effect of the drug. Despite challenging and unsettling experiences, some continue participating repeatedly. Of significance, healthy volunteer's coping strategies are also embedded in lived experiences of the clinical trial itself, which I now turn to.

8. Experiential knowledge as a way of building trust

The basis of participants' continued involvement and trust seems strongly dependent on positive or negative experiences. For most, taking part in a trial free of adverse drug effects motivated them to return. This common theme is well articulated here: '... I have done these (clinical trials) for a long time now and have never had any (unexpected side effects) so I guess it makes you feel more comfortable I guess ...'.

Such positive experiences become the basis on which future decisions made. A clinical drug trial without any adverse drug reactions, meant the likelihood of repeat participation: '... certain factors determine your involvement, you know. Your past experience if all went well, and staff were nice ..., and how good the facilities [are]' (Todd). However, note how reference to staff being nice sits in contradiction to claims that the process is fraught with surveillance and restrictions. For some participants, experiences were not just about having a trial free of adverse effects but about relations with the staff and the quality of facilities. Power relations come into play as being treated well by staff was often seen as the sign of professional expertise and worth referencing when considering further participation. As Zoltan puts it: 'they always treat me nice and kind, they sometimes call me to find out how I am or to invite me to another trial ...'. Here trust does not just develop from

information packs and media reports but reflects the experience of being treated as a valuable part of the clinical trial process. For these participants, positive experiences meant that risks were seen as normal in a 'usual or everyday sense' (Peretti-Watel, 2014):

'... there are risks, but so is life in general, one has to do what they have to do in life to make ends meet, you know, so it doesn't worry me at all. Yes, I do think about "what ifs" [what if a trial goes wrong] but I do that in most things in my life' (Wallace)

Touchwood nothing bad has happened to me so far. So (I go into the trial) believing that nothing bad will ever happen to you. You will always be fine ... and you do see things (risks) as normal (Neil)

Perceived positive experiences become bases on which future involvement and perceptions of safety are established. In terms of 'becoming-with', involvement is a complicated process as individuals begin to include their bodily experiences or lack of it as evidence of safety. Some participants start to escalate their involvement by taking part in trials they previously avoided.

'... before I got on to the first trial I did some research ... but for the second one ... I did not even bother. The third again I didn't bother. I thought it was going to be fine ...' (James).

James' account was shared among participants; most talked of adopting a cautious approach by conducting personal research on the trial drugs but escalated involvement and lowered their guard the more trials they participated in without adverse effects. This is captured in Neil's reflection on why he did not do any further research on subsequent drug trials:

You start to think, because the people doing it [conducting the clinical trial] are professionals, and then you know they can be trusted, you know, to do their job right ... then I am more likely to do it again and worry less. I trust that they know what needs to be done (Neil).

Notably, this 'lowering of their guard' occurs in a context where professionals claim the clinical trials are safe. At this point for volunteers, risk becomes absent. There is temporary loss of mistrust in that they begin to take these positive 'uneventful' experiences as markers of safety as well as future reference points of what constitutes risky trials. Predictably, they start to see professionals and institutions as vested in their well-being and thus worth trusting.

I trust that they would be honest ... and give me the support I need. I don't think they would lie, otherwise, it will damage their image and reputation (John).

I have some trust in these people, in the institutions doing their studies. When you are on the trial, you only have one option but trust they are your friends at that particular moment. So, you have to trust them (Neil).

Between them, John and Neil had taken part in 15 clinical trials and at the time of the interview had expressed interest in further clinical trial participation. Pertinent here is how their views are not based on consent or information; they trust assuming that their safety guarantees good professional practice. Not a simple relationship between two parties, this should be seen in the context of the broader assemblage of trust, including governance processes, social relations and circumstances.

However, for some, negative experiences drew them to question the process, affecting perceptions of the professionals' expertise and abilities:

'Immediately after that [experiencing unexpected side effects], I was thinking I cannot trust the researchers they don't know what they are doing' (John)

[After experiencing unexpected side effects]. It makes me lose confidence in the trial maker's ability to know everything about the drug and its effects, and I do not trust them fully after this. I am

becoming cynical. There is a limit to what they can know or predict and that makes me more hesitant (Wallace)

It is important to note that John earlier talked about trusting researchers and the process as unavoidable, however, experiencing unexpected side effects led him to question the researchers' abilities. He still continued participating in clinical trials with his doubts nonetheless. After this experience, Wallace stopped taking part in what he considered "risky" phase trials, opting instead to participate in the perceived "less risky" flu vaccine trials. Note how this change in perception is predicated on bodily experiences of trial drug side effects. Such experiences may not result in complete loss of trust in institutions or clinical drug trial process but a more cautious approach. This highlights temporality and fluidity (Rhodes et al., 2016) of trust as an assemblage. For some, experiencing severe expected or unexpected adverse effects led to broader questions about safety and underlined the reality of risks:

I have had some experiences like three or four times, where some of us were told to go back home because someone [healthy volunteer] had some unexpected side effect to the drugs. Some of those were quite serious but obviously, we were not told the extent or how serious. So, kind of lucky it wasn't me really but it's common (Jake).

What we experienced was unexpected and out of this world. It was akin to being on LSD [or] marijuana. It was noticeable in such things as hallucinations and loss of track of time, lying in bed for five hours. And you are not aware of it, giggling and laughing ... but yeah, it was crazy and scary and worried ... because it wasn't included in the list ... but I have done a couple more after that (Jules).

Note in Jake's account reference to 'three or four times' and Jules' 'I have done a couple after that', indicating that experiencing adverse effects did not discourage participation. For other participants, un/expected adverse effects were explained away as bad luck or the significance of the problem was underplayed:

I was very lucky. I only developed a blood clot on the last day and it was only a 12 cm one, which within 24 hours was down to 3 cm. I was, lucky I did panic a bit but at the same time, I was, like, it was the last day of dosing ... I know some had, like, five or six blood clots, and big, but the clots were on the sites of the cannula stretching upwards, and everyone was panicking, saying if it moves to your heart or brain, you may have a stroke or something like that. It was scary, you know, and maybe I am putting it mildly when I say I panicked a little. (Kristof).

The presence or lack of unexpected adverse effects on bodies become the basis on which healthy volunteers start to trust or question safety in clinical trials, illustrating how repeat volunteering is not a single bounded event but a process evolving with time - participants vacillating between trust and mistrust. Becoming a repeat healthy volunteer does not necessarily entail a fixed state of understanding or perceiving risks as normal or acceptable. Rather it is a state of constant flux where negotiating trust and mistrust is constant.

9. Discussion and conclusion

This research provides an understanding of trust among repeat healthy volunteers. It contributes to sociological research by Abadie (2010); Elliott (2008) and Fisher (2015) among others, who have over the years illustrated how repeat volunteering occurs among disenfranchised populations in the US. This research extends this notion, by demonstrating the role of trust among healthy volunteers in the UK, who are employed, yet engage in the risky business of healthy volunteering to make ends meet. The paper demonstrates how healthy volunteers rationalise repeat participation in clinical drug trials.

Moving away from a sole focus on rationality, this paper has attempted to move us to consider trust as entailing a process involving

decision-making located in wider social networks and relations. As Corrigan (2003) argued, informed consent is a social - not just objective - process. From the participants accounts trust is illustrated as constituting an uncertain, fragile and unpredictable contingency. Sociological work demonstrates a need to rethink fixed processes of consent and recruitment as they limit understanding of the processes that lead to trust and repeat volunteering. This stance suggests taking a 'careful' approach (Puig de la Bellacasa, 2011; Dennis, 2017), aware that the world around shapes people's views and experiences in clinical drug trials and consequently for some brings about trust, mistrust and repeat volunteering. One limitation of current approaches to maintaining trust and trial recruitment from a CRO perspective, has been over-emphasising structural interventions and policies to improve practices (Hudson et al., 2016) such as the informed consent process (Corrigan, 2003) with little attention on how individuals experience and negotiate involvement in clinical drug trials and how they come to trust or mistrust in these processes. Dennis (2017) and Ahmed (2004) highlight contingency, in a classic Latin meaning of (*Latin: contingere: com-, with; tangere, to touch*) linked to proximity, to get close enough to touch another and to be moved by another (Ahmed, 2004, p. 28). Dennis (2017) develops this by calling for an existential awareness of how individual affect inside relates to the social world outside. In terms of healthy volunteer experiences, I suggest an awareness of relations involved in the clinical trial process between self and others, including the materiality of the drugs themselves and their role. Trust should not be seen as an isolated act of rational actors; rather rationality itself is embedded in a complex assemblage of relations between participants, feelings, experiences with the drugs and other actors in this process. This assemblage acts as a basis for knowledge brought to decision-making processes and claims to trust/mistrust in the clinical drug trial process.

While a focus on the ideal capable individual with human liberties as the universal moral principle for guiding discussions in clinical drug trials is useful, there is need to consider the 'effect of different programmes and campaigns on individuals' capacity for freedom and ethical self-formation' (Keane, 2003, p. 231; p. 231). This means reconsidering human involvement in clinical trials beyond objective facts and risk assessments made by rational informed actors as a 'matter of concern' (Latour, 2004) whereby what constitutes trusting action becomes open to critical consideration by rethinking trust as an assemblage involving socio-economic circumstances, bodily experiences and sensations of adverse effects and relations. Consequently, the process is less about facts than 'becoming-with' (Deleuze, 2004; Dennis, 2017) wherein analysis of trust and mistrust takes into account that seemingly individual acts occur in complex relational, processual, uncertain and unstable 'events'. Trust in repeat volunteering is not a bounded event but shaped by broader networks, including 'what gets made in research and practice alike, and the bodily boundaries we inevitably bring into being' (Dennis, 2017, p.14; p.14). This necessitates further sociological discussions about trust to include broader issues on how trust is established in the interactions within and outside the clinical trial processes as participants 'become-with' repeat healthy volunteering.

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